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| 10/532,948 | 01/09/2006 | Shigeyuki Yokoyama | P/2850-106 | 2037 |

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OSTROLENK FABER GERB & SOFFEN
1180 AVENUE OF THE AMERICAS
NEW YORK, NY 100368403

| EXAMINER | |
|---|---|
| GEBREYESUS, KAGNEW H | |
| ART UNIT | PAPER NUMBER |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/532,948 | YOKOYAMA ET AL. | |
| | Examiner | Art Unit | |
| | Kagnew H. Gebreyesus | 1656 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1 and 6-16* is/are pending in the application.

4a) Of the above claim(s) *8-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6 and 7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's response on August 17, 2007 to the Office Action dated February 26, 2007 is acknowledged. Applicants have cancelled claims 2-5. Claims 8-16 are withdrawn without prejudice. Claims 1, 6 and 7 are amended. Claims 1, 6 and 7 are present for examination.

### *Claim Rejections - 35 USC § 101*

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1,6 and 7 are rejected under 35 U.S.C. 101 because the claimed inventions are directed to non-statutory subject matter. As broadly interpreted, the claims contain embodiments that encompass producing proteins in cells within a multi-cellular organism including humans. This embodiment is considered unethical and unacceptable to the public. Applicants may amend the claims to recite "an isolated cell".

### *Withdrawn - Objection to Specification*

The objection to the abstract is withdrawn following Applicants amendments.

The disclosure was objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 20 of the specification. This objection is hereby withdrawn.

Furthermore the objection with regards to the title of the invention is withdrawn following Applicants amendment to the title.

The specification now complies with 37 CFR 1.821-1-825 because Applicants have assigned SEQ ID NOs. to the two nucleotide sequences (representing tRNA molecules in figure 2) and a polypeptide sequence (comprising 424 amino acids in figure 8) are now assigned SEQ ID NOs.

***Withdrawn -Claim Objections***

The objection to claim 1 and 7 are withdrawn following applicants claim amendments.

***Withdrawn - Claim Rejections - 35 USC § 112***

Claim 4 was rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 4 has been cancelled therefore the rejection is moot.

***Withdrawn - Claim Rejections - 35 USC § 112***

Claims 1-7 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection has been withdrawn following Applicants claim amendments.

Claims 1-7 were further rejected under 35 U.S.C. 112, first paragraph, for not being enabled for the scope encompassed. However this rejection has been withdrawn following Applicants claim amendments.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6 and 7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method expressing a protein comprising a non-naturally occurring amino acid comprising expressing said protein in an isolated animal cell, does not reasonably provide enablement for a method of expressing a protein comprising a non-naturally occurring amino acid in an animal cell wherein said cell can be in any animal including humans. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988). The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill

of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claims encompass using a tyrosyl tRNA synthetase mutant (ORS) that can be expressed in an animal cell wherein the cell can be in a whole organism such as a human in view of producing a protein comprising an unnatural amino acid(s).

The specification provides guidance and examples for expressing specific mutant tyrosyl tRNA synthetase molecules such as the V37C195 mutant in an isolated animal cell in the presence of an amber suppressor tRNA (O-tRNA) comprising a partial sequence from *Bacillus stearothermophilus* and a human tRNA gene (specification page 28) to produce a protein comprising the unnatural amino acid 3-iodotyrosine. However, the specification does not teach a method expressing said ORS and O-tRNA in an animal cell wherein the cell is comprised within an animal as broadly encompassed by the claims.

. Claim 1, 6 and 7 are so broad as to encompass animal cells transformed with the specific mutant tyrosyl tRNA synthetase and an amber suppressor $tRNA^{Tyr}$, in cells within any multi-cellular organism including in humans. While methods for transforming cells *in vitro* are well known in the art, methods for successfully transforming cells within complex multicellular organisms are not routine and are highly unpredictable. Furthermore, methods for producing a successfully transformed cell in isolated cells are unlikely to be applicable to producing recombinant proteins comprising unnatural amino acids in any multicellular organisms such that a transgenic animal is produced.

However, in this case the disclosure is limited to producing a protein comprising an unnatural amino acid in isolated cells. Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including the use of transgenic animal cells to produce a protein comprising an unnatural amino acid. The standard for meeting the enablement requirement is whether one of skill in the art can make the invention without undue experimentation. The amount of experimentation to make the claimed invention is enormous and undue.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, expression of a protein in an animal is unpredictable the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is suggested that applicants limit the claims to "An isolated eukaryotic cell ...".

***Withdrawn -Claim Rejections - 35 USC § 102***

Claims 1-7 were rejected under 35 U.S.C. 102(a) as being anticipated by Sakamoto et al. (Site-specific incorporation of an unnatural amino acid into proteins in mammalian cells, Nucleic Acids Research. Nov. 01, 2002. Vol.30, No. 21; pg. 4692).

Applicant's argument and priority document has been considered and found to be persuasive. The rejection of claims 1-7 as being anticipated under 35 U.S.C. 102(a) by Sakamoto et al is withdrawn.

Claims 1-3, 6-7 were rejected under 35 U.S.C. 102(a) as being anticipated by Schultz et al (Application 10/126,931 now US PAT 7083970). This rejection has been withdrawn following Applicant's claim amendments.

***Maintained -Claim Rejections - 35 USC § 103***

Claims 1-7 were rejected under 35 U.S.C. 103(a) as being unpatentable over Kiga et al (An Engineered Escherichia coli tyrosyl-tRNA synthetase for Site Specific incorporation of an unnatural amino acid into proteins in Eukaryotic translation and its application in wheat germ cell-free systems. PNAS July 23, 2002).

Kiga et al teach tyrosyl tRNA from Escherichia coli (E. Coli) was engineered to preferentially recognize 3-iodo-L-tyrosine rather than L-tyrosine for the site-specific incorporation of 3-iodo-L-tyrosine into proteins in eukaryotic translation systems.

The response argues:

As indicated above, claim 1 of the application has been amended to incorporate the recitations of pending claims 3 and 4, as well as the sequence information regarding TyrRS. Thus, as now amended, the subject claim recites (in sub-paragraph "B") the expression of suppressor tRNA originating in Bacillus stearothermophilus capable of binding with [the] tyrosine derivatives (i.e., discussed in sub-paragraph "A") in the presence of mutant tyrosyl tRNA synthetase. In contrast to the invention, Kiga et al. discloses the use of suppressor tRNA originating from E. coli in the in vitro translation system. The expression of suppressor tRNA, however, originating from Bacillus stearothermophilus in animal cells as recited in claim 1 is nowhere taught or even suggested in the subject Kiga et al. reference.

Applicant's argument has been carefully considered but not found persuasive because an expression method to produce a protein comprising an unnatural amino acid using an *E. coli* mutant tRNA synthetase (V37C195) and an amber suppressor tRNA from *Bacillus stearothermophilus* is obvious over the disclosure of Kiga et al who

teach the same method using *E. coli* mutant tRNA synthetase (V37C195) and an amber suppressor tRNA from *E. coli*. Furthermore Kiga et al suggest that the use of their translation system must be expanded to include mammalian cells (page 9720, second column, last paragraph). Therefore both the motivation and the suggestion for the use of animal cell to produce eukaryotic proteins of interest are found in Kiga et al's teachings.

Kiga et do not teach an amber suppressor tRNA from *Bacillus stearothermophilus*. However, for expression purposes one of ordinary skill in the art can be motivated to use any amber tRNA derived from a microorganism such as a *Bacillus species* that contains both the A and the B box, structures necessary for expression of the tRNA in Eukaryotic cells.

The response further argues:

> "Further in support of this distinction between the invention as claimed and the disclosure contained in Kiga et al., the Examiner's attention is respectfully directed to Fig. 4A. The Figure demonstrates that suppressor tRNA originating from E. coli, i.e., as according to the reference, did not work for the purpose recited in applicants' claims in animal cells. See, e.g., lane 4 with reference to the description set forth on pp. 48-50 of the present specification and, in particular, the paragraph bridging pp. 49-50".

However this argument is not found persuasive because Kiga et al have shown a method of producing a protein comprising the unnatural amino acid 3-iodo-L-tyrosine using the *E. coli* V37C195 mutant tRNA synthetase (ORS) and an amber suppressor tRNA from *E. coli* in a Eukaryotic translation system (see fig. 2, lane 3). Applicants do not present data that show that the vector comprising an amber suppressor tRNA from *E. coli* was successfully transfected in any eukaryotic cell. Kiga et al's method is a cell free system that does not require transfecting vectors into a eukaryotic cell thus

provides evidence that the *E. coli* amber suppressor tRNA can function with the V37C195 mutant tRNA synthetase from *E. coli*. For this reason Applicants argument suggesting that the *E. coli* amber suppressor does not function in conjunction with the *E. coli* mutant ORS is not found persuasive.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kagnew H. Gebreyesus whose telephone number is 571-272-2937. The examiner can normally be reached on 8:30am-5: 30pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kagnew H.Gebreyesus PhD.
Nov. 12, 2007.
KHG

/Nashed/
Nashaat T. Nashed, Ph. D.
Primary Examiner
Art Unit 1656